DOP69

Tofacitinib in ulcerative colitis: Early 'real-world' experience from four UK tertiary centres

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Background: Tofacitinib is a partially selective Janus kinase inhibitor that was approved for the treatment of refractory moderate to severe ulcerative colitis (UC) in 2018. We report the real-world clinical effectiveness and adverse effects of tofacitinib in UC.

Methods: We conducted a retrospective observational cohort study of tofacitinib-treated patients with UC between October 2018 to October 2019 from 4 UK centres. Disease activity was assessed using the Simple Clinical Colitis Activity Index (SCCAI) or Partial Mayo Score (PMS) depending on the study site. Response and remission were defined at week 8 and 26 as a reduction in SCCAI or PMS of ≥3, and SCCAI <3 or PMS <2, respectively. Corticosteroid-free remission was defined as remission with no corticosteroid use at the time of assessment irrespective of baseline corticosteroid status.

Results: We included 140 patients (65% M; median age 37y [range 16–81]) with a median disease duration of 5.5y (IQR 2.2–11.8). Forty-six per cent (65/140) were receiving corticosteroids at baseline and 83% (116/140) had previously received at least one biologic (62 anti-TNF, 4 vedolizumab, 50 both). Median (IQR) serum CRP and faecal calprotectin levels at baseline were 4 mg/l (1.6–15) and 540 µg/g (316–1175).

Table 1. Summary of all-causality and treatment-related TEAEs, and TEAEs by SOC (safety analysis set)

	All-causality TEAEs in participants receiving PF-06480605 500 mg IV n (%)	Treatment-related TEAEs in participants receiving PF-06480605 500 mg IV n (%)
All-causality TEAEs		
Participants evaluable for AEs	50 (100.0)	50 (100.0)
Participants with AEs	33 (66.0)	8 (16.0)
Participants with SAEs	3[a] (6.0)	1[a] (2.0)
Participants discontinued due to AEs	3[b] (6.0)	1[b] (2.0)
TEAEs by SOC		
Blood and lymphatic system disorders	2 (4.0)	0 (0.0)
Cardiac disorders	2 (4.0)	0 (0.0)
Ear and labyrinth disorders	2 (4.0)	1 (2.0)
Endocrine disorders	1 (2.0)	0 (0.0)
Gastrointestinal disorders	14 (28.0)	2 (4.0)
General disorders and administration-site conditions	7 (14.0)	2 (4.0)
Infections and infestations	13 (26.0)	0 (0.0)
Injury, poisoning and procedural complications	5 (10.0)	0 (0.0)
Investigations	6 (12.0)	1 (2.0)
Metabolism and nutrition disorders	1 (2.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	9 (18.0)	2 (4.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (4.0)	1 (2.0)
Nervous system disorders	1 (2.0)	1 (2.0)
Respiratory, thoracic and mediastinal disorders	3 (6.0)	1 (2.0)
Skin and subcutaneous tissue disorders	7 (14.0)	2 (4.0)
Vascular disorders	4 (8.0)	2 (4.0)

[a]Three participants experienced four SAEs: UC and peritonitis in one participant (not treatment-related), UC in one participant (not treatment-related) and alopecia in one participant (treatment-related)

[b]One participant permanently discontinued the study drug and the study due to UC (not treatment-related), one discontinued the study drug due to UC (not treatment-related) and one discontinued the study drug due to alopecia (treatment-related)

IV, intravenous; n, number of participants in the specified category; N, number of participants overall (safety population); SAE, serious adverse event; SD, standard deviation; SOC, system organ class; TEAE, treatment-emergent adverse event

Table 2. UMVUE and MLE analyses of endoscopic improvement at Week 14 in participants treated with PF-06480605 500 mg IV (Per-protocol, observed cases)

Analysis	Endoscopic subscore at baseline	N	n	Endoscopic improvement rate (%)	p-value[a] (one-sided Pr > Z)	95% CI
UMVUE	2/3	45	17	38.2	<0.001	23.82, 53.68
MLE	2/3	45	17	37.8	<0.0001	23.77, 53.46[b]
	2	5	3	60.0	<0.0001	14.66, 94.73[b]
	3	40	14	35.0	<0.0001[a]	20.63, 51.68[b]

[a]p-values were computed for the testing of the null hypothesis of 6% for endoscopic improvement rate at Week 14
[b]Clopper-Pearson method was used for 95% CI in the MLE analyses

CI, confidence interval; IV, intravenous; MLE, maximum likelihood estimator; N, number of participants overall (per-protocol population); n, number of participants with endoscopic improvement; UMVUE, uniformly minimum-variance unbiased estimator

Response and remission rates were 73% (81/111) and 56% (62/111) respectively at week 8 (median ΔSCCAI of –3 [IQR -6 to -1], median ΔPMS –4 [–6 to –1]) and 48% (39/82) and 39% (32/82) respectively at week 26 (median ΔSCCAI –3 [IQR –7 to –1], median ΔPMS –4 [–6 to –1]). Steroid-free remission was seen in 47% (52/111) and 37% (30/82) patients at week 8 and 26. Patients with response or remission had a significantly lower CRP ($p = 0.02$) but not calprotectin ($p = 0.38$) levels at baseline. Response and remission rates were no different stratified by prior biologic use ($p = 0.56$). Treatment was discontinued after a median of 3 months (IQR 2–4) in 43 patients: 32 with primary non-response, 9 loss of response and in 1 each because of an adverse drug reaction (headache) and patient choice. 7/17 patients had a clinical response to dose re-escalation following a loss of response on dose reduction. The median time to dose de-escalation was 67 (IQR 25–240) days. Seven patients were hospitalised and 5 underwent colectomy. Six serious infections were noted including 2 herpes zoster infections but there were no venous thromboembolic events. Median total cholesterol, low-density lipoprotein and high-density lipoprotein increased from 4.4 mmol/l (IQR 3.7–5.2), 2.47 (1.9–2.9) and 1.5 (1.1–1.9) to 4.8 mmol/l (4.1–6.0), 2.8 (2.13.5) and 1.7 (1.4–1.9) respectively after 8 weeks of tofacitinib.

Conclusion: PF-06480605 exhibited an acceptable safety and tolerability profile and statistically significant EI in participants with moderate to severe UC. These results warrant further evaluation in subsequent studies.

DOP70

High-dimensional analysis reveals a novel signature for IL-17 producing CD8 T cells in inflammatory bowel disease

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Background: The pathogenesis of IBD has previously mainly been associated with a dysregulation of CD4 T-cell responses, and active disease is linked to induction of pathogenic IL-17 producing T helper cells. Importantly, CD8 T cells can also produce IL-17 and demonstrate a significant increase in active IBD. However, it remains unclear whether this is due to conventional or unconventional T-cell responses and whether these CD8 responses could play a role as novel biomarkers or therapeutic targets of active IBD.

Methods: We isolated lymphocytes from the peripheral blood and intestinal tissue of IBD patients ($n = 56$) and performed a detailed analysis of CD8 T-cell phenotype and function using high-parametric flow cytometry and mass cytometry in combination with algorithm-aided bioinformatic analysis.

Results: We observe a significant increase in IL-17 production by CD8 T cells in active IBD, primarily produced by conventional CD8 T cells. Unconventional T-cell subsets (e.g. MAIT cells, γδ T cells and NKT cells) represented only ~30% (peripheral blood) or ~25% (intestinal tissue) of IL-17 producing CD8 T cells (Tc17). The mass cytometric analysis identified Tc17 cells as a distinct cell population within the intestinal CD8 T-cell compartment that can be further subdivided into 3 subsets which share expression of phenotypic markers such as CD6, CD39, CD69 and PD1 and a low expression of CD27. This novel signature was validated in a separate cohort of IBD patients. Moreover, at initial IBD diagnosis, the IL-17 signature is associated with flare-free survival in a retrospective cohort analysis based on published transcriptome data.

Conclusion: Our data indicate that conventional IL-17 producing CD8 T cells are a very distinct cell population that is linked to IBD activity. The identification of a novel IL-17 CD8 signature may help guide treatment decisions as a biomarker and for immunotherapeutic approaches.

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Efficacy, safety, and tolerability of ustekinumab in paediatric patients with moderately to severely active Crohn's disease: Results from, UniStar, a phase 1 study

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